RIC

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

15270C-000420PC

Date of mailing *(day/month/year)* 25 MAR 2009

Applicant's or agent's file reference	FOR FURTHER ACTION
15270C-4-2PC	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/80382	17 October 2008 (17.10.2008)	17 October 2007 (17.10.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/00; C07K 16/18 (2009.01)
USPC - 424/133.1, 530/387.3

Applicant ELAN PHARMA INTERNATIONAL LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered. 6/25/09

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220. 8/17/09

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450	08 March 2009 (08.03.2009)	Lee W. Young PCT Helpdesk: 571-272-4300
Facsimile No. 571-273-3201		PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

Uncocketed
Transcribed Noted
Not Docketed
Abandoned
Action: Resp to Written OP
Due: 8/17/09
By: PGS

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☒ in electronic form

   c. time of filing/furnishing

      ☒ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 4-9 and 61-63

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4-9 and 61-63 are so unclear that no meaningful opinion could be formed *(specify)*:
Claims 4-9 and 61-63 are multiple dependent claims under PCT Rule 6.4(a) and they are not drafted in accordance with the second and third sentenced of PCT Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 4-9 and 61-63

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I claim 1- 3, 10-60, and 64-133 are directed to a method of treating Alzheimer's disease, and related diseases relative to the absence of ApoE4 alleles.

Group II claims 134-136 are directed to humanized form of a 10D5 antibody.

Group III claims 137-139 are directed to a humanized form of a 12A11 antibody.

Group IV claims 140-142 are directed to a humanized form of a 3D6 antibody.

Group V claim 143 is directed to a humanized antibody comprising a humanized light chain having an amino acid sequence comprising SEQ 10 NO:48 and a humanized heavy chain having an amino acid sequence comprising SEQ ID NO:66 or SEQ ID NO:67.

Group VI claim 144 is directed to an isolated nucleic acid having a sequence comprising SEQ ID NO:68 provided that residues 1-57 encoding a signal sequence mayor may not be present.

Group VII claims 145-146 are directed to an isolated humanized antibody comprising a mature light chain variable region sequence of SEQ ID NO:2 and a mature heavy chain variable region sequence of SEQ ID NO:3, and a human heavy chain constant region of IgG isotype with L234A, L235A, and G237A mutations, wherein positions are numbered by the EU numbering system.

Group VIII claims 147-148 are directed to an isolated humanized form of a 12B4 antibody, wherein the 12B4 antibody is characterized by a light chain variable region sequence of SEQ ID NO:31, and heavy chain variable region sequence of SEQ ID NO:32, and a human heavy chain constant region of IgG isotype with L234A, L235A, and G237A mutations, wherein positions are numbered by the EU numbering system.

Group IX claims 149-151 are directed to a humanized form of a 266 antibody (ATCC accession number PTA6123) comprising a human heavy chain constant region with L234A, L235A and G237A mutations, wherein positions are numbered by the EU numbering system.

Group X claims 152-160 are directed to an isolated antibody comprising a human heavy chain constant region of isotype IgG1, wherein amino acids at positions 234, 235, and 237 (EU numbering) are each alanine.
Group XI claims 161- 193 are directed to a method and a kit for determining a regime for bapineuzumab administration.

Group XII claims 194-195 are directed to a method for improving the safety of bapineuzumab.

**********Continued in supplemental box**********

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1- 3, 10-60, 64-133, 143, and 145-146

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	See Below	YES
	Claims	See Below	NO
Inventive step (IS)	Claims	88, 96, 100, 105, 109, 120, 122, 143	YES
	Claims	See Below	NO
Industrial applicability (IA)	Claims	1-3, 10-60, 64-133, 143, 145-146	YES
	Claims	None	NO

2. Citations and explanations:

Novelty: Claims 14, 22, 26, 29, 33-60, 64-96, 99-100, 104-110, 117-120, 122-127, 132,143 (YES)

1-3, 10-13, 15-21, 23-25, 27-28, 30-32, 97-98, 101-103, 111-116, 121, 128-131, 133, and 145-146 (NO)

Inventive step: 1-3, 10-60, 64-87, 89-95, 97-99, 101-104, 106-108, 110-119, 121, 123-133, 145-146 (NO)

Claims 1-3, 10-13, 15-21, 23-25, 27-28, 30-32, 97-98, 101-103, 111-116, 121, 128-131, 133, and 145-146 lack novelty under PCT Article 33(2) as being anticipated by US 2006/0280743 A1 to Basi et al. (hereinafter 'Basi').

Regarding claim 1, Basi discloses a method of treating Alzheimer's disease, comprising administering to a patient (para [0201] - administering an effective dosage of an antibody) having zero ApoE4 alleles ("ApoE4 non-carrier patient") (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) and Alzheimer's disease (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), an effective regime of an antibody that specifically binds to e N-terminal epitope of A.beta.(para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta).

Regarding claim 2, Besi further discloses the method of claim 1, wherein antibody specifically binds to an epitope within:
residues 1-7 of A.beta (para [0201] - antibodies that specifically bind to an epitope within residues 1-7 of A.beta);
residues 1-5 of A.beta (para [0201] - antibodies that specifically bind to an epitope within residues 1-5 of A.beta) ; or
residues 3-7 of A.beta. (para [0201] - or antibodies that specifically bind to an epitope within residues 3-7 of A.beta.)

Regarding claim 3, Basi further discloses the method of claim 1 or claim 2, wherein a dosage of the antibody within a range of about 0.15 mg/kg to about 2 mg/kg (para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1 -10 mg/kg, preferably at least 1 mg/kg) is administered by intravenous infusion (para [0220] - intravenous infusion are preferred for administration of antibody).

Regarding claim 10, Basi discloses a method of treating Alzheimer's disease (para [0035] - the invention features e method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), comprising administering (para [0201] - administering an effective dosage of an antibody) to an ApoE4 non-carrier patient (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) an antibody that specifically recognizes the N-terminal region of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) in a regime (para [0216] - Antibody is usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly) effective to maintain a mean serum concentration of the antibody in the range of about 0.1 mu.g/ml to about 60 mu.g/ml (para [0274] - This Example demonstrates that when held at modest serum concentrations, 25-70 .mu.g/ml, the antibodies gained access to the CNS at levels sufficient to decorate .beta.-amyloid plaques).

**********Continued in supplemental box**********

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:
Box No. IV (Lack of unity of invention)

The shared technical feature of Groups I, XI and XII is identifying patients having no ApoE4 alleles exhibiting various brain diseases, including, inter alia, Alzheimer's disease. However, this is not an improvement over the prior art of US 5773220 A to DeKoskey et al. (30 June 1998) that specifically teaches identifying patients having no ApoE4 alleles exhibiting various brain diseases, including, inter alia, Alzheimer's disease (abstract, col 2 ln 5-20). Groups II-X are directed to various polypeptide sequences and/or nucleic acid sequences that share no common technical feature with each other or with Groups I, XI and XII, and do not relate to a single general inventive concept because, under PCT Rule 13.2, the different nucleotides or polypeptides represented by the nucleic acid sequences or amino acid sequences are not common to one another but are different because they are composed of unique structural sequences.

Note that Claim Nos. 4-9 and 61-63 have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V No 2 (citations and explanations)

Regarding claim 11, Basi further discloses the method of claim 10, wherein the maximum serum concentration of the antibody in the patient less than about 28 .mu.g antibody/ml serum (para [0274] - This Example demonstrates that when held at modest serum concentrations, 25-70 .mu.g/ml, the antibodies gained access to the CNS at levels sufficient to decorate .beta.-amyloid plaques).

Regarding claim 12, Basi further discloses the method of claim 10, wherein the maximum serum concentration is within a range of about 4-28 .mu.g antibody/ml serum (para [0274] - This Example demonstrates that when held at modest serum concentrations, 25-70 .mu.g/ml, the antibodies gained access to the CNS at levels sufficient to decorate .beta.-amyloid plaques).

Regarding claim 13, Basi further discloses the method of claim 10, wherein the antibody is a humanized form of a mouse 3D6 antibody (ATCC accession number PTA-5130) (para [0114] - the present invention features a humanized antibody to the N-terminus of A.beta. A particularly preferred starting material for production of humanized antibodies is 3D6; para [0012] - an alignment of the amino acid sequences of the light chain of mouse 3D6, humanized 3D6; para [0350] - The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130), and positions 234,235 and 237 in the heavy chain constant region are occupied by Ala, Ala and Ala respectively (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ala) indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

Regarding claim 15, Basi discloses e method of treating Alzheimer's disease (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), comprising administering (para [0201] - administering an effective dosage of an antibody) to an ApoE4 non-carrier patient (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) an antibody that specifically recognizes the N-terminal region of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) in a regime (para [0216] - Antibody is usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly) effective to achieve a mean plasma anti-A.beta. antibody concentration of at least 450 pg/ml (para [0216] - dosage is adjusted to achieve a plasma antibody concentration of 1-1000 .mu.g/ml and in some methods 25-300 .mu.g/ml; para [0005] - The normal concentration of A.beta. in human plasma is typically in the range of 50-200 pg/ml; Specification [0099] - The area under the curve (AUC) is the area under the curve in a plot of concentration of drug in plasma against time).

Regarding claim 16, Basi further discloses the method of claim 15, wherein the mean plasma anti-A.beta. antibody concentration is in the range of about 600 pg/ml to about 3000 pg/ml (para [0216] - dosage is adjusted to achieve a plasma antibody concentration of 1-1000 .mu.g/ml and in some methods 25-300 .mu.g/ml; para [0005] - The normal concentration of A.beta. in human plasma is typically in the range of 50-200 pg/ml; Specification [0099] - The area under the curve (AUC) is the area under the curve in a plot of concentration of drug in plasma against time).

Regarding claim 17, Basi discloses a method of treating Alzheimer's disease (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), comprising administering (para [0201] - administering an effective dosage of an antibody) to an ApoE4 non-carrier patient (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) an antibody that specifically recognizes the N-terminal region of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) in a regime (para [0216] - Antibody is usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly) effective to achieve a mean plasma anti-A.beta. antibody concentration of at least 450 pg/ml (para [0216] - dosage is adjusted to achieve a plasma antibody concentration of 1-1000 .mu.g/ml and in some methods 25-300 .mu.g/ml; para [0005] - The normal concentration of A.beta. in human plasma is typically in the range of 50-200 pg/ml; Specification [0099] - The area under the curve (AUC) is the area under the curve in a plot of concentration of drug in plasma against time).

Regarding claim 18, Basi further discloses the method of claim 17, wherein the mean plasma anti-A.beta. antibody concentration is in the range of about 600 pg/ml to about 3000 pg/ml (para [0216] - dosage is adjusted to achieve a plasma antibody concentration of 1-1000 .mu.g/ml and in some methods 25-300 .mu.g/ml; para [0005] - The normal concentration of A.beta. in human plasma is typically in the range of 50-200 pg/ml; Specification [0099] - The area under the curve (AUC) is the area under the curve in a plot of concentration of drug in plasma against time).

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 19, Basi discloses a method of reducing cognitive decline in a patient (para [0199] - The present invention is directed inter alia to treatment of Alzheimer's and other amyloidogenic diseases, e.g.,
treating or preventing cognitive decline in the patient) having zero ApoE4 alleles ("ApoE4 non-carrier patient") (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4), comprising administering to the patient an antibody that specifically binds to an N-tenninal epitope of A.beta (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) in a regime effective to reduce the cognitive decline of the patient relative (para [0199] - improving cognitive function, and/or reversing, treating or preventing cognitive decline) to a control patient to whom the antibody is not administered (para [0232] - Measured values of the level or profile in a patient after administering a therapeutic agent are then compared with the control value; para [0232] - A significant increase relative to the control value (e.g., greater than one standard deviation from the mean) signals a positive or sufficient treatment outcome);
wherein: the ApoE4 non-carrier patient and control patient have been diagnosed with mild to moderate Alzheimer's disease (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms); and the cognitive decline is measured by MMSE (para [0337] - Baseline scores on suitable metrics including the MMSE and the ADAS together with other metrics designed to evaluate a more normal population are collected; para [0335] - Suitable patients score in the 12-26 range on the Mini-Mental State Exam (MMSE)).

Regarding claim 20, Basi further discloses the method of claim 19, wherein the antibody is administered by intravenous infusion (para [0220] - intravenous infusion are preferred for administration of antibody) at a dosage within a range of about 0.15 mg/kg to about 2 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg).

Regarding claim 21, Basi further discloses the method of claim 19 or claim 20, wherein the antibody is a
humanized form of a mouse 3D6 antibody (ATCC PTA-5130) (para [0114] - the present invention features a humanized antibody to the N-terminus of A.beta. A particularly preferred starting material for production of humanized antibodies is 3D6; para [0012] - an alignment of the amino acid sequences of the light chain of mouse 3D6, humanized 3D6; para [0350] - The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130), and positions 234,235 and 237 in the heavy chain constant region are occupied by Ala, Ala and Ala respectively (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ala) indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Humen Services (1991)).

Regarding claims 23, Basi discloses a method of reducing brain volume decline in a patient (para [0201] - the invention provides methods of preventing or treating a disease associated with amyloid deposits of A.beta. in the brain of e patient. Such diseases include Alzheimer's disease, Down's syndrome and cognitive impairment) having zero ApoE4 alleles ("ApoE4 non-carrier patient") (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4), comprising administering to the ApoE4 non-carrier patient an antibody that
specifically binds to an N-terminal epitope of A.beta (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) in a regime effective to reduce the brain volume decline of the ApoE4 non-carrier patient (para [0199] - improving cognitive function, and/or reversing, treating or preventing cognitive decline; para [0238] - monitoring, over the course of treatment, any art-recognized physiologic symptom For example, one can monitor cognitive impairment. The latter is a symptom of Alzheimer's disease and Down's syndrome) relative to a control patient to whom the antibody is not administered (para [0232] - Measured values of the level or profile in a patient after administering a therapeutic agent are then compared with the control value; pare [0232] - A significant increase relative to the control value (e.g., greater than one standard deviation from the mean) signels a positive or sufficient treatment outcome);
wherein the ApoE4 non-carrier patient and control patient have been diagnosed with mild to moderate Alzheimer's disease (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms).

Regarding claim 24, Basi further discloses the method of claim 23, wherein the antibody is administered by intravenous infusion (para [0220] - intravenous infusion are preferred for administration of antibody) at a dosage within a range of about 0.15 mg/kg to about 2 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 25, Basi further discloses the method of claim 23 or claim 24, wherein the antibody is a humanized form of a mouse 3D6 antibody (ATCC PTA-5130), (para [0114] - the present invention features a humanized antibody to the N-terminus of A.beta. A particularly preferred starting material for production of humanized antibodies is 3D6; para [0012] - an alignment of the amino acid sequences of the light chain of mouse 3D6, humanized 3D6; para [0350] - The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130), and positions 234,235 and 237 in the heavy chain constant region are occupied by Ala, Ala and Ala respectively (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ala) indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

Regarding claim 27, Basi further discloses the method of claim 23, wherein the brain volume decline is measured by MRI (para [0335] - Disease progression can also be monitored by MRI).

Regarding claims 28, Basi discloses a method of treating Alzheimer's disease (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), comprising subcutaneously administering to a patient having the disease (para [0220] - Therapeutic agents can be administered by subcutaneous) and one or two copies of an ApoE4 allele ((para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) an effective regime of an antibody that binds to an N-terminel epitope of A.beta.(pere [0201] - administering en effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta).

Regarding claim 30, Basi further discloses the method of claim 28, wherein the antibody is administered at a dose of 0.01-0.6 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg) and a frequency of between weekly and monthly (para [0215] - exemplary treatment regimes enteil administration once per every two weeks or once a month).

Regarding claim 31, Basi further discloses the method of claim 28, wherein the antibody is administered at a dose of 0.05-0.5 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg).

Regarding claim 32, Basi further discloses the method of claim 28, wherein the antibody is administered at a dose of 1-40 mg (para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg) and a frequency of between weekly end monthly (para [0215] - exemplary treatment regimes entail administration once per every two weeks or once a month).

Regerding claim 97, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patient (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease; pare [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) , comprising administering to the patient an antibody that specifically binds to an epitope within residues 1-11 of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) to a patient having one or two ApoE4 alleles (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4), wherein the antibody is administered in a regime in which 0.15-1 mg/kg of antibody (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg) is administered quarterly (para [0215] - exemplary treatment regimes entail administration once every 3 months) by intravenous administration (para [0220] - intravenous infusion are preferred for administration of antibody), or at e dose frequency and route of administration that generates an equivalent average serum concentration or area under the curve (para [0216] - dosage is adjusted to achieve a plasma antibody concentration of 1-1000 .mu.g/ml and in some methods 25-300 .mu.g/ml).

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Regarding claim 98, Basi further discloses the method of claim 97, wherein the antibody is a humanized form of a mouse 3D6 antibody (ATCC accession number PTA-5130) (para [0114] - the present invention features a humanized antibody to the N-terminus of A.beta. A particularly preferred starting material for production of humanized antibodies is 3D6; para [0012] - an alignment of the amino acid sequences of the light chain of mouse 3D6, humanized 3D6; para [0350] - The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130), and positions 234,235 and 237 in the heavy chain constant region are occupied by Ala, Ala and Ala respectively (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ala) indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

Regarding claim 101, Basi further discloses the method of claim 97, whereln the dose is 0.5 mg/kg (para [0215] - usually 0.01 to 5 mg/kg. of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg).

RRegarding claim 102, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patient (para [0035] - the invention feetures e method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), comprising administering to the patient an antibody that specifically binds to en epitope within residues 1-11 of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) to a patient having zero ApoE4 alleles (para [0208] - Patients amenable to tratment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4), wherein the dose of the antibody is 0.5-2 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example doseges can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg) administered quarterly (para [0215] - exemplery treatment regimes entail administration once every 3 months) by intravenous administration (para [0220] - intravenous infusion ere preferred for administration of antibody), or a dose frequency and route of administration that generates an equivalent serum concentration or area under the curve (para [0216] - dosage Is adjusted to achieve a plasma antibody concentration of 1-1000 .mu.g/ml and in some methods 25-300 .mu.g/ml).

Regarding claim 103, Basi further discloses the method of claim 102, wherein the antibody is a humanized form of a mouse 3D6 antibody (ATCC eccession number PTA-5130) (para [0114] - the present invention features a humanized antibody to the N-terminus of A.beta. A particularly preferred starting meteriel for production of humanized antibodies is 3D6; para [0012] - an alignment of the amino acid sequences of the light chain of mouse 3D6, humenized 3D6; para [0350] - The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130), and positions 234,235 and 237 in the heevy chain constant region are occupied by Ala, Ala and Aie respectively (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ale) Indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative subetitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabet numbering system Is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

Regarding claim 111, Basi discloses a method of effecting prophylaxis of a disease characterized by
deposits of A.beta. deposits in the brain of a patient (para [0035] - the invention features a method of preventing or treating an emyloidogenic disease, e.g., Alzheimer's disease; para [0057] - Alzheimer's disease is en example of a "disease cherectenzed by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) comprising administering an effective regime of an agent thet is en antibody to A.beta. to a patient (para [0201] - administering an effective dosage of en entibody that specifically binds to an epitope within residues 1-10 of A.beta), wherein the patient has at least one ApoE4 allele (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4).

Regarding claim 112, Basi further discloses the method of claim 111, wherein the patient has two ApoE4 elleles (para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4).

Regarding claim 113, Basi further discloses the method of claim 111, wherein the patient is asymptomatic (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms).

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Regarding claim 114, Basi further discloses the method of claim 111, wherein the patient has a mini-mental test score of 27 or higher (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0335] - Suitable patients score in the 12-26 range on the Mini-Mental State Exam (MMSE)).

Regarding claim 115, Basi further discloses the method of claim 111, wherein the patient has a mini-mental test score of 20-26 (para [0335] - Suitable patients score in the 12-26 range on the Mini-Mental State Exam (MMSE)).

Regarding claim 116, Basi further discloses the method of claim 111, wherein the patient is at least sixty years of age (para [0209] - In asymptomatic patients, treatment can begin at any age. Usually, however, it is not necessary to begin treatment until a patient reaches 60 or 70).

Regarding claim 121, Basi disclose a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), comprising administering an antibody that specifically binds to an epitope within residues 1-11 of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) and has mutations in the constant region that reduce binding to an Fc receptor to the patient (para [0172] - a corresponding change in a human antibody hinge sequence can be made if reduced Fc.gamma.I receptor binding is desired; para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease), wherein the antibody is administered at the same dose and/or frequency to each patient (para [0215] - two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated; para [0217] - The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic) regardless of the number of ApoE4 alleles in the patient (para [0209] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4).

Regarding claim 128, Basi discloses a method of treating or effecting prophylaxis of a disease characterized by A.beta. deposits in the brain of patient (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease; para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) comprising administering an effective regime of a humanized antibody to the patient (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta; para [0204] - The antibodies used in such methods can be humanized); wherein the humanized antibody comprises e meture light chain variable region sequence of SEQ ID NO:2 (SEQ ID NO: 71, which is 100% identical to SEQ ID NO: 2), and e meture heavy chain variable region sequence of SEQ ID NO:3 (SEQ ID NO: 72, which is 100% identical to SEQ ID NO: 3), end e human heavy chein constent of IgGl isotype (para [0074] - Human isotype IgG1 is preferred because of it having highest affinity of human isotypes for the FcRI receptor on phegocytic cells) with L234A, L235A, and G237A mutations (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replecing residues 234, 236 or 237 by Ale) indicate thet elterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinetions such es gly, ele), wherein positions ere numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

Regarding claim 129, Basi further discloses the method of claim 128, wherein the patient has at least one ApoE4 allele (para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4).

Regarding claims 130 and 131, Basi further discloses the method of claim 128, wherein the dose is 0.15-1 mg/kg or 0.15-2 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg).

Regarding claim 133, Besi further discloses the method of cleim 128, for treating e population of the patients wherein the regime administered to different patients in the population does not depend on
the number of ApoE4 alleles present in a patient, because Basi teaches different regime can be used (para [0215] - An exemplery treatment entails administration in multiple dosages over a prolonged period, for example, of at least six months. Additional exemplery treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1 -10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly. In some methods. two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated), without mentioning ApoE4.

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Regarding claim 145, Basi discloses an isolated humanized antibody comprising a mature light chain variable region sequence of SEQ ID NO:2 (SEQ ID NO: 71, which is 100% identical to SEQ ID NO: 2) and a mature heavy chain variable region sequence of SEQ ID NO:3 (SEQ ID NO: 72, which is 100% identical to SEQ ID NO: 3), and a human heavy chain constant region of IgG isotype with L234A, L235A, and G237A mutations (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ala) indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

Regarding claim 146, Basi further discloses the isolated antibody of claim 145 that has human IgG1 isotype (para [0074] - Human isotype IgG1 is preferred because of it having highest affinity of human isotypes for the FcRI receptor on phagocytic cells).

Claims 14, 22, 26, 99, and 104 lack an inventive step under PCT Article 33(3) as being obvious over Basi, as above, in view of US 2007/0196375 A1 to Tobinick.

Regarding claim 14, Besi discloses a method of treating Alzheimer's disease, comprising administering to an ApoE4 non-carrier patient an antibody that specifically recognizes the N-terminal region of A.beta., as discussed in claim 10. However, Basi does not specifically teach wherein the antibody is bapineuzumb. Tobinick discloses a method of treating Alzheimer's diseases (para [0267] - This category includes, but is not limited to Alzheimer's Diseese, Humens with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Tobinick, to obtain the method of Basi, wherein the antibody is bapineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed in order to use the humanized monoclonal antibody Bapineuzumab to treat Alzheimer's disease, because Basi teeches a method of treating Alzheimer's disease comprising administering to an ApoE4 non-carrier patient an antibody that specifically recognizes the N-terminal region of A.beta., while Tobinick teaches a method of treating Alzheimer's diseases using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 22, Basi discloses e method of reducing cognitive decline in a patient having zero ApoE4 alleles, comprising administering to the patient en antibody thet specifically binds to an N-tenninal epitope of A.beta, as discussed in claim 19. However, Basi does not specifically teech wherein the antibody is bapineuzumab. Tobinick discloses a method of treating amnestic mild cognitive impairment (para [0267] - This category includes, but is not limited to Alzheimer's Disease, amnestic mild cognitive impairment, Humans with these disorders are amenable to treatment utilizing perispinal administretion without direct Intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Tobinick, to obtain the method of Basi, wherein the antibody is bapineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed in order to use the humanized monoclonal antibody Bapineuzumab to reduce cognitive decline in a patient having zero ApoE4 alleles, because Basi teaches e method of reducing cognitive decline in a patient having zero ApoE4 alleles, comprising administering to the patient an antibody that specifically binds to en N-tenninel epitope of A.beta, while Tobinick teaches a method of treating amnestic mild cognitive impairment using a humanized monoclonal antibody, Bapineuzumab, egainst A.beta.

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Regarding claim 26, Basi discloses a method of reducing brain volume decline in a patient having zero ApoE4 alleles, comprising administering to the ApoE4 non-carrier patient an antibody that specifically binds to an N-tenninal epitope of A.beta, as discussed in claim 23. However, Basi does not specifically teach wherein the antibody is bapineuzumab. Tobinick discloses a method of treating dementia including Alzheimer's Disease and amnestic mild cognitive impairment (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, amnestic mild cognitive impairment, vascular dementia, and mixed dementia Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Tobinick, to obtain the method of Basi, wherein the antibody is bapineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed in order to use the humanized monoclonal antibody Bapineuzumab to reduce brain volume decline in a patient having zero ApoE4 alleles, because Basi teaches a method of reducing brain volume decline in a patient having zero ApoE4 alleles, comprising administering to the patient an antibody that specifically binds to an N-tenninal epitope of A.beta, while Tobinick teaches a method of treating treating dementia including Alzheimer's Disease and amnestic mild cognitive impairment using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 99, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patient, comprising administering to the patient having one or two ApoE4 alleles an antibody that specifically binds to an epitope within residues 1-11 of A.bete., es discussed in claim 97. However, Basi does not specifically teach wherein the antibody is bapineuzumab. Tobinick discloses e method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Diseese, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Tobinick, to obtain the method of Basi, wherein the antibody is bapineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed, in order to use the humanized monoclonal antibody Bapineuzumab to treat or effect prophylaxis of Alzheimer's disease in a patient having one or two ApoE4 alleles, because Basi teaches a method of treating or effecting prophylaxis of Alzheimer's disease in a patient having one or two ApoE4 alleles, comprising administering to the patient an antibody that specifically binds to an epitope within residues 1-11 of A.beta, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 104, Basi discloses e method of treating or effecting prophylaxis of Alzheimer's disease in a patient, comprising administering to the patient heving zero ApoE4 alleles en antibody that specifically binds to an epitope within residues 1-11 of A.beta., as discussed in cleim 102. However, Besi does not specifically teech wherein the antibody is bapineuzumeb. Tobinick discloses a method of treating Alzheimer's Diseese (pere [0267] - Dementie. This category includes, but is not limited to Alzheimer's Disease, Humens with these disorders are amenable to treatment utilizing perispinal administration without direct intrethecal injection of lerge molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, e humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Tobinick, to obtain the method of Basi, wherein the antibody is bapineuzumeb, besed on the teaching of Tobinick, to obtain the invention as claimed, in order to use the humanized monoclonal antibody Bapineuzumab to treat or effect prophylexis of Alzheimer's disease in a patient having zero ApoE4 alleles, because Basi teaches a method of treating or effecting prophylexis of Alzheimer's disease in a patient having zero ApoE4 alleles, comprising administering to the patient an antibody that specifically binds to an epitope within residues 1-11 of A.beta, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monocional antibody, Bapineuzumab, against A.beta.

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Claims 29, 33- 47, 49-59, 64-65, 71-86, 89-93, 106-107, 110, 117-119, 123-127, and 132 lack an inventive step under PCT Article 33(3) as being obvious over Basi, as above, in view of an article entitled "Course of cerebral amyloid angiopathy--related inflammation" by Kinnecom et al. (hereinafter 'Kinnecom').

Regarding claims 29 and 33, Basi discloses a method of treating Alzheimer's disease, comprising subcutaneously administering to a patient having the disease and one or two copies of an ApoE4 allele an effective regime of an antibody that binds to an N-terminal epitope of A.beta., as discussed in claim 28. However, Basi does not specifically teaches the method further comprising monitoring for vasogenic edema. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises monitoring for vasogenic edema, based on the teaching of Kinneocm, to obtain the invention as claimed, in order to control the development of vasogenic edema in the Alzheimer's patients treated with antibody against A.beta, because Basi teaches a method of treating Alzheimer's disease in a patient comprising subcutaneously administering to a patient having the disease and one or two copies of an ApoE4 allele an effective regime of an antibody that binds to an N-terminal epitope of A.beta., while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele.

Regarding claim 34, Basi discloses a method of treating Alzheimer's disease (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease), comprising administering to a patient having the disease (para [0201] - administering an effective dosage of an antibody) and one or two ApoE4 alleles (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) an effective regime of an antibody that binds to an N-terminal epitope of A.beta.(para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta). However, Basi dose not specifically teach administering a corticosteroid to the patient to treat vasogenic edema arising from the administration of the antibody. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema; pg 1416, col 1: anti-A monoclonal antibody infusion in patients with AD revealed similar reversible hyperintense lesions in three subjects and associated cognitive changes In one, raising the possibility that passive immunization to A.beta. may be associated with some of the same vascular effects as active immunization), which can be treated with corticosteroid (pg 1413, col 2: One patient experienced two recurrences of symptoms, primarily subacute cognitive decline, with prompt response to corticosteroid after the first event). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to extend the method of Basi, wherein the method further comprises administering a corticosteroid to the patient to treat vasogenic edema arising from the administration of the antibody, based on the teaching of Kinnecom, to obtain the invention as claimed in order to use the method of Basi, wherein the method further comprises administering a corticosteroid to the patient to treat vasogenic edema arising from the administration of the antibody to treat patients with Alzheimer's disease, because Basi teaches a method of treating patients with Alzheimer's disease comprises administering to a patient having the disease effective regime of an antibody that binds to an N-terminal epitope of A.beta, while Kinnecom teaches that patients with Alzheimer's disease receiving antibodies against A.beta can develop vasogenic edema , which can be treated by administering a corticosteroid.

Regarding claim 35, Kinnecom further discloses the method of claim 34, further comprising monitoring the patient for vasogenic edema (pg 1414, col 1: MRI appearance and correlation with clinical course; Fig 1).

Regarding claim 36, although Kinnecom does not specifically teaches the method of claim 34, wherein the dose or frequency of administration of the antibody is reduced or eliminated during the vasogenic edema relative to the dose or frequency before the vasogenic edema, this limitation is further obvious because it is clinical routine practice to eliminate or reduce dose or frequency of administration of a therapeutic agent when a severe symptom developed during the treatment. Kinnecom teaches the symptom of vasogenic edema includes cognitive symptoms and seizures (Abstract), which is a life threating symptom. Therefore, one of ordinary skill in the art at the time the invention was made would have known to eliminate, or reduce the dose or frequency of administration of the antibody during the vasogenic edema in comparison with the dose or frequency used before the vasogenic edema.

Regarding claim 37, although Kinnecom does not specifically teach the method of claim 34, wherein the dose or frequency of administration of the antibody is increased after resolution of the vasogenic edema relative to the dose or frequency during the vasogenic edema, this limitation is further obvious because it is clinical routine practice to resume the treatment after the side effect symptom due to a treatment is controlled. Therefore, one of ordinary skill in the art at the time the invention was made would have known to increase the dose or frequency of administration of the antibody after resolution of the vasogenic edema relative to the dose or frequency during the vasogenic edema.

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Regarding claim 38, Basi discloses a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease (para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) characterized by amyloid deposits of A.beta. in the brain (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient), comprising:
administering different regimes to different patients in the population (para [0215] - exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1 -10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly; para [0217] - The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic; para [0215] - two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated);
wherein at least one of the regimes comprises administering an antibody to A.beta. to a patient (para [0216] - Intervals can also be irregular as indicated by measuring blood levels of antibody to A.beta). However, Basi does not specifically teach administering different regimes to different patients in the population depending on which allelic forms of ApoE are present in the patients. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein administering different regimes to different patients in the population depending on which allelic forms of ApoE are present in the patients, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to control the development of vasogenic edema in the Alzheimer's patients treated with antibody against A.beta, because Basi teaches a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to use special regime for treating Alzheimer's patients having ApoE4 allele.

Regarding claim 39, Basi further discloses the method of claim 38, wherein a first regime comprises administering an antibody to A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta) to a patient having zero copies of an ApoE4 allele (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4). Although none of inventors specifically teaches the second regime lacks an antibody to A.beta. and is administered to patients having one or two copies of an ApoE4 allele, this limitation is further obvious because Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to use regime lacking an antibody to A.beta. for treating Alzheimer's patients having ApoE4 allele in order to prevent vasogenic edema from happening.

Regarding claim 40, although none of inventors specifically teaches the differences between the first and second regimes, based on the teaching of Kinnecom that Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para), one of ordinary skill in the art at the time the invention was made would have known to use the second regime with reduced antibody or antibody activities to A.beta. for treating Alzheimer's patients having ApoE4 allele when including an antibody to A.beta.in the second regime, in order to prevent vasogenic edema from happening. Therefore, the method of claim 38, wherein the different regimes comprise first and second regimes each comprises administering an antibody to A.beta; and the second regime differs from the first regime in at least one of (i) - (vi) below:
(i) the dose of the antibody is reduced;
(ii) the frequency of administration of the antibody is reduced;
(iii) the capacity of the antibody to induce a clearing response to amyloid deposits is reduced;
(iv) the mean serum concentration of the antibody is reduced;
(v) the maximum serum concentration of the antibody is reduced;
(vi) the time of initiation of treatment relative to disease progression is earlier; whereby the first and second regimes are administered such that at least one of (a), (b) and (c) occurs:
(a) the second regime is administered in patients having two copies of an ApoE4 allele and the first regime in patients having zero copies of an ApoE4 allele;
(b) the second regime is administered in patients having one copy of an ApoE4 allele and the first regime in patients having zero copies of an ApoE4 allele; and/or
(c) the second regime is administered in patients having two copies of an ApoE4 allele and the first regime is administered to patients having one copy of an ApoE4 allele.

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Regarding claim 41, Basi further discloses the method of claim 40, wherein a first regime comprises administering an antibody to A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A beta) to a patient having zero copies of an ApoE4 allele (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4). Although none of inventors specifically teaches the second regime comprises administering a second antibody to A.beta. and the second antibody has reduced binding to an Fcgamma receptor relative to the first antibody and is administered to patients having one or two copies of an ApoE4 allele, this limitation is further obvious because Basi further teaches an antibody has reduced binding to an Fcgamma receptor relative to the first antibody (para [0172] - a corresponding change in a human antibody hinge sequence can be made if reduced Fc.gamma.I receptor binding is desired); while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to use the second regima comprising an antibody has reduced binding to an Fcgamma receptor relative to the first antibody to A.beta., for treating Alzheimer's patients having one or two copies of an ApoE4 allele in order to prevent vasogenic edema from happening.

Regarding claims 42, Basi further discloses the method of claim 41, wherein the second antibody has one or more mutations in the constant region that reduce binding to the Fcgamma receptor the mutations not being present in the first antibody (para [0174] - the antibodies of the invention can also have an altered Fc region with altered binding affinity for Fc.gamma.RI as compared with the unmodified antibody).

Regarding claims 43-45, Basi furthar discloses the method of claim 42, wherein the one or more mutations is/are at position(s) in a heavy chain constant region selected from the group consisting of positions 234,235,236 and 237 (para [0174] - Mutations on adjacent or close sites in the hinge link region, a.g., replacing rasiduas 234, 236 or 237 by Ala, indicate that alterations in rasiduas 234, 235, 236, and 237 at least affect affinity) (ED numbering) (para [0171] - Typically the Kabat numbering system is used to indicata which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (saa ganarally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Sarvicas (1991)), and wherein the one or more mutations are L234A, L235A and G237A (para [0174] - Mutations on adjacent or close sites in the hinga link region (e.g., replacing rasidues 234, 236 or 237 by Ala) indicate that allarations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala; para [0013] - FIG. 2 depicts an alignment of the amino acid saquencas of the heavy chain of mouse 3D6, humanized 3D6; Fig. 2).

Regarding claim 46, Basi further discloses the method of any of claims 42-45, wherein the isotype of the constant region is human IgG 1 (para [0074] - Humen isotype IgG1 is praferred because of it having highest affinity of human isotypes for the FcRI receptor on phagocytic cells).

Regarding claim 47, Besi further discloses the method of any of claims 42-45, wherein the isotype of the constant region is human IgG4 (para [0085] - segments of the genes from a mouse monoclonel entibody may ua joinad to human constant (C) segments, such as IgG1 and IgG4).

Regarding claim 49, Basi further discloses the method of claim 40, wherein e first regime comprises administaring an antibody to A.beta. (para [0201] - administering en effective dosege of en entibody thet specifically binds to an epitope within residues 1-10 of A.beta), which is a human IgG1 isotype (pera [0074] - Human isotype IgG1 is preferred because of it having highest affinity of human isotypes for the FcRI receptor on phegocytic celis), and to e petient heving zero copies of an ApoE4 allele (para [0208] - Petients emenable to treatment include individuels at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4). Although none of inventors specifically teaches the second regima comprises administering e second antibody to A.beta. end the second entibody is human IgG4 isotype, end is administered to patients having one or two copies of an ApoE4 allele, this limitation is further obvious because Basi further teaches en humanized antibody to A.beta. can be human IgG1 or IgG4 isotype (para [0085] - segments of the ganas from a mouse monoclonel antibody may be joined to human constant (C) segments, such es IgG1 and IgG4), whereas human IgG1 isotype has highest affinity for FcRI receptor (para [0074] - Human isotype IgG1 is preferred because of it heving highest affinity of human isotypes for the FcRI receptor on phagocytic cells); while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to use the second regime comprising an antibody has reduced reduced afinity to FcRI receptor, IgG4, relative to the first entibody, IgG1, to A.beta., for treating Alzheimer's patients having one or two copies of an ApoE4 allele in order to prevent vasogenic edema from happening.

Regarding claim 50, Basi further discloses the method of claim 38, wherein the disease is Alzheimer's disease (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease).

Regarding claim 51, although none of inventors specifically teach the method of claim 38, further comprising determining which alleles of ApoE are present in the patient, this limitation is further obvious because Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to determine which alleles of ApoE are present in the patient before using an antibody to A.beta. for treating patients with Alzheimer's disease, in order to prevent vasogenic edema from happening.

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Regarding claim 52, Basi further discloses the method of claim 38, wherein the different regimes
differ in dose of the antibody administered (para [0215] - exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1 -10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly).

Regarding claim 53, Basi further discloses the method of claim 38, wherein the different regimes
differ in frequency of the antibody administered (para [0215] - exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1 -10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly).

Regarding claim 54, Basi further discloses the method of claim 38, wherein the different regimes
differ in the type of antibody administered (para [0215] - two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated).

Regarding claim 55, although none of inventors specifically teaches the differences between the first and second regimes of claim 40, based on the teaching of Kinnecom that Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para), one of ordinary skill in the art at the time the invention was made would have known to use the second regime with reduced antibody or antibody activities to A.bate. for treating Alzheimer's patients having higher copy number(s) of ApoE4 allele when including an antibody to A.beta.in the second regime, in order to prevent vasogenic edema from happening. Therefore, the method of claim 40, wherein the dose of the antibody and/or the frequency of administration of the antibody and/or the capacity of the emtibody to induce a clearing response to amyloid deposits is reduced in (a) patients having two ApoE4 alleles relative to patients having one ApoE4 allele; and/or (b) patients having one copy of an ApoE4 allele relative to petients having zero copies of en ApoE4 allele, and/or (c) patients having two copies of an ApoE4 allele relative to patients heving one copy of an ApoE4 allele.

Regarding claim 56, although none of inventors specifically teaches the differences between the first and second regimes of claim 40, based on the teaching of Kinnecom that Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para), one of ordinary skill in the art at the time the invention was made would have known to use the second regime with reduced antibody or antibody activities to A.beta. for treating Alzheimer's patients having higher copy number(s) of ApoE4 allele when including an antibody to A.beta.in the second regime, in order to prevent vasogenic edema from happening. Therefore, the method of claim 40, wherein the dose of the agent and/or the frequency of administration of the agent and/or the capacity of the agent to induce a clearing response to amyloid deposits is reduced in patients having one or two ApoE4 alleles relative to patients having zero ApoE4 alleles of an ApoE4 allele.

Regarding claim 57, Basi further teeches the method of claim 38, wherein patients in different population
are administered a dose of 0.15-1 mg/kg or a dose of 0.5-2 mg/kg of an antibody (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg)
specifically binding within rasidues 1-11 of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta). Although Basi does not specifically teach patients in the population having one or two ApoE4 alleles are administered a lower dose, this limitation is further obvious bacausa because Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to use regime with lower dose of an antibody to A.beta. for treating Alzheimer's patients having ApoE4 allele in order to prevent vasogenic edema from happening. Therefore, the method of claim 38, patients in the population having one or two ApoE4 alleles are administered a dose of 0.15-1 mg/kg, and patients in the population having zero ApoE4 alleles are administered a dose of 0.5-2 mg/kg of an antibody specifically binding within residues 1-11 of A.beta.

Regarding claim 58, although none of inventors specifically teach the method of claim 40, wherein the patients in the population having one or two ApoE4 alleles are administered a lower dosage of agent than
patients having zero ApoE4 alleles until vasogenic edema has appeared and resolved, and the
same dosage of agent thereafter, this limitation is further obvious because Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to lower dosage of agent for treating patients having one or two ApoE4 alleles than treating patients having zero ApoE4 alleles until vasogenic edema has appeared and resolved. It is one of clinical strategies to use the same dosage of agent thereafter.

Regarding claim 59, although none of inventors specifically teach the method of claim 40, wherein the patients in the population having one or two ApoE4 alleles are administered a lower frequency of the agent than the patients having zero ApoE4 alleles until vasogenic edema has appeared and resolved,
and the same dosage of agent thereafter, this limitation is further obvious because Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to reduce frequency of the agent for treating patients having one or two ApoE4 alleles than treating patients having zero ApoE4 alleles until vasogenic edema has appeared and resolved. It is one of clinical strategies to use the same dosage of agent thereafter.

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Regarding claim 64, Basi further discloses the method of claim 38, wherein the antibody binds to an epitope within residues 1-11 of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta).

Regarding claim 65, Basi further discloses the method of claim 64, wherein the antibody has human IgG1 isotype (para [0074] - Human isotype IgG1 is preferred because of it having highest affinity of human isotypes for the FcRI receptor on phagocytic cells).

Regarding claim 71, Basi further discloses the method of claim 38 or claim 40, wherein the antibody is a humanized 266 (para [0075] - antibodies include those binding to epitopes with residues 10-15, 15-20, 25-30, 10-20, 20, 30, or 10-25 of A.beta; para [0010] - humanized antibodies having improved binding affinities and/or reduced immunogenicity, when used as therapeutic reagents; Specification: para [00201] - Another exemplary antibody is a humanized 266 antibody or variant thereof. The 266 antibody binds to an epitope between residues 13-28 of A.beta).

Regarding claim 72, Basi discloses a method of treating or effecting prophylaxis of a disease (para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) characterized by amyloid deposits in the brain in the patient (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient), comprising:
administering different regimes to different patients (para [0215] - exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1 -10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly; para [0217] - The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic; para [0215] - two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated); wherein at least one of the first and second regimes comprises administering an antibody to A.beta (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta; para [0216] - Intervals can also be irregular as indicated by measuring blood levels of antibody to A.beta). However, Basi does not specifically teach use of a measurement of ApoE4 copy number for selecting different regimes for treatment or prophylaxis of a disease characterized by amyloid deposits in the brain in the patient. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2; CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein use of a measurement of ApoE4 copy number is selected for determining different regimes for treatment or prophylaxis of a disease characterized by amyloid deposits in the brain in the patient, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to control the development of vasogenic edeme in the Alzheimer's patients treated with antibody against A.beta, because Basi teaches a method of treating or effecting prophylaxis a disease characterized by amyloid deposits in the brain in the patient using different regimes, wherein at least one of the first and second regimes comprises administering an antibody to A.beta, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to use a measurement of ApoE4 copy number for selecting different regimes for treatment or prophylaxis of a disease characterized by amyloid deposits in the brain in the patient.

Regarding claim 73, although none of inventors specifically teaches the differences between the first and second regimes, based on the teaching of Kinnecom that Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para), one of ordinary skill in the art at the time the invention was made would have known to use the second regime with reduced antibody or entibody ecitivties to A.beta. for treating Alzheimer's patients having ApoE4 allele when including an antibody to A.beta.in the second regime, in order to prevent vasogenic edeme from happening. Therefore, use of claim 72, wherein the different regimes comprise e first regime and a second regime, wherein the first and second regimes each comprise administering an
antibody to A.beta. and the second regime differs from the first regime in et least one of (i) to (vi) below:
(i) the dose of the antibody is reduced
(ii) the frequency of administration of the antibody is reduced;
(iii) the capacity of the antibody agent to induce a clearing response to amyloid deposits is reduced;
(iv) the mean serum concentration of the antibody is reduced;
(v) the maximum serum concentration of the antibody is reduced;
(iv) the time of initiation of treatment relative to disease progression is earlier; whereby at least one of (a) to (c) occurs:
(a) the second regime is administered patients having two copies of an ApoE4 allele and the first regime to patients having zero copies of an ApoE4 allele,
(b) the second regime is administered to patients having one copy of an ApoE4 allele and the first regime to patients having zero copies of an ApoE4 allele; and
(c) the second regime is administered to patients having two copies of an ApoE4 allele and the first regime to patients having one copy of an ApoE4.

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Regarding claim 74, Basi discloses the manufacture of a medicament for treating Alzheimer's disease (para [0199] - the disclosed immunological reagents (e.g., humanized immunoglobulins) in the manufacture of a medicament for the treatment or prevention of an amyloidogenic disease), wherein the medicament comprises an antibody to A.beta. (para [0199] - treatment of Alzheimer's and other amyloidogenic diseases by administration of therapeutic immunological reagents (e.g., humanized immunoglobulins) to specific epitopes within A.beta.). However, Basi does not specifically teaches use of a measurement of ApoE4 copy number in the manufacture of a medicament to treat Alzheimer's disease. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the manufacture of the medicament of Basi, wherein the manufacture of the medicament further comprises use of a measurement of ApoE4 copy number in the manufacture of a medicament, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to manufacture different medicaments comprising antibody against A.beta directed by the copy numbers of ApoE4 allele for treating Alzheimer's patients having one or two copies of an ApoE4 allele to prevent the development of vasogenic edema from happening, because Basi teaches the manufacture of a medicament for treating Alzheimer's disease, wherein the medicament comprises an antibody to A.beta., while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to manufacture medicaments with reduced antibody or entibody activities to A.beta. for treating Alzheimer's patients having ApoE4 allele.

Regarding claim 75, Basi discloses a method of monitoring (para [0209] - Treatment can be monitored by assaying antibody levels over time) a population of patients undergoing treatment
or prophylaxis for a disease (para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) characterized by amyloid deposits of A.beta in the brain (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) with an antibody to A.beta (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta). However, Basi does not specifically teach the method comprising: performing different monitoring regimes in different patients in the population for vasogenic edema. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method comprises performing different monitoring regimes in different patients in the population for vasogenic edema, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to use the method of Basi for more specifically motoring of population of patients having one or two copies of an ApoE4 allele for preventing the development of vasogenic edema while treated with an antibody to A.beta , because Basi teaches a method of monitoring a population of patients undergoing treatment or prophylaxis for a disease characterized by amyloid deposits of A.bete. in the brain with an antibody to A.beta., while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to perform different monitoring regimes in different patients in the population for vasogenic edema, with special attention paid to population of patients having ApoE4 allele to achieve, wherein the frequency of monitoring is greater for:
(a) patients having two copies of ApoE4 relative to patients having zero copies of ApoE4;
(b) patients having one copy of an ApoE4 allele relative to patients having zero copies of an ApoE4 allele; and/or
(c) patients having two copies of an ApoE4 allele relative to patients heving one copy of an ApoE4 allele.

Regarding claim 76, Basi further discloses the method of cleim 75, wherein the disease is Alzheimer's disease (para [0035] - the invention features a method of preventing or trealing en emyloidogenic disease, e.g., Alzheimer's disease).

Regarding claim 77, Kinnecom further discloses the method of cleim 75, further comprising determining which eilelic forms of ApoE ere present in each patient in the population (Teble 1).

Regarding claims 78-79, both Basi and Kinnecom further disclosea the method of claim 77, wherein the monitoring is by brain imaging, MRI (Basi: para [0335] - Disease progression can also be monitored by MRI; Kinnecom: pg 1414, col 1 - MRI appearance and correlation with clinical course).

Regarding claims 80-83, for the same reason discussed in claim 75, one of ordinary skill in the art at the time the invention was made would have known to perform different monitoring regimes in different patients in the population for vasogenic edema, with special attention paid to population of patients having ApoE4 allele. Therefore: the method of claim 75, wherein patients having one ApoE4 allele are monitored more frequently than patients having zero ApoE4 alleles;
patients having two ApoE4 alleles are monitored more frequently than patients having one ApoE4 allele;
patients having one ApoE4 allele are monitored more frequently than patients having zero ApoE4 alleles.
patients having zero ApoE4 alleles are not monitored by MRI for vasogenic edema.

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Regarding claim 84, Basi discloses t method of monitoring (para [0209] - Treatment can be monitored by assaying antibody levels over time) a population of patients undergoing treatment or prophylaxis for a disease (para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) characterized by amyloid deposits of A.beta. in the brain (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) with an agent that induces an antibody to A.beta. (para [0191] - Immune responses against amyloid deposits can also be induced by administration of nucleic acids encoding antibodies and their component chains used for passive immunization). However, Basi does not specifically teach the method comprising: performing different monitoring regimes in different patients in the population for vasogenic edema. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method comprises performing different monitoring regimes in different patients in the population for vasogenic edema, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to use the method of Basi for more specifically motoring of population of patients having one or two copies of an ApoE4 allele for preventing the development of vasogenic edema while treated with an antibody to A.beta , becouse Basi teaches a method of monitoring a population of patients undergoing treatment or prophylaxis for a disease characterized by amyloid deposits of A.beta. in the brain with an antibody to A.beta., while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to perform different monitoring regimes in different patients in the population for vasogenic edema, with special attention paid to population of patients having ApoE4 allele to achieve, wherein the frequency of monitoring is greater for:
(a) patients having two copies of ApoE4 relative to patients having zero copies of ApoE4;
(b) patients having one copy of an ApoE4 allele relative to patients having zero copies of an ApoE4 allele; and/or
(c) patients having two copies of an ApoE4 allele relative to patients having one copy of an ApoE4 allele.

Regarding claim 85, Basi discloses a method of treating or effecting prophylaxis of a patient (para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) for e disease characterized by amyloid deposits of A.beta. in the brain (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient), comprising administering to a patient with at least one ApoE4 allele (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptome, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) an antibody to an epitope within residue 1-11 of A.beta (para [0201] - administering an effective dosege of an antibody thet specifically binds to an epitope within residues 1-10 of A.beta) or an agent that induces such an antibody to A.bete. (para [0191] - Immune responses against amyloid deposite can also be induced by administration of nucleic acids encoding antibodies and their component chains used for passive immunization), and monitoring the patient by MRI (para [0335] - Disease progression can also be monitored by MRI). However, Basi does not specifically teach monitoring the patient for vasogenic edema. Kinnecom discloses e clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/4 genotype; pg 1415, col 1, lest para). It would have been obvious to one of ordinary skill in the art at the time the invention wes made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises monitoring for vasogenic edema by MRI, based on the teachings of Basi and Kinnecom, to obtain the invention as claimed, in order to control the development of vesogenic edeme in the Alzheimer's patients heving at least one ApoE4 allele treated with antibody egainst A.bete, becauso Basi teeches a method of treeting or effecting prophylexis of a petient for a disease cheracterized by amyloid deposits of A.beta in the brain, comprising administering to a petient with at leest one ApoE4 allele en entibody to an epitope within residue 1-11 of A.bete., and monitoring the petient by MRI, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vesogenic edema, which is associated with ApoE4 allele.

Regarding claim 86, Basi further discloses the method of claim 85, wherein the entibody is a humanized form of a mouse 3D6 antibody (ATCC accession number PTA-5130) (para [0114] - the present invention features e humenized entibody to the N-terminus of A.beta. A particularly preferred starting material for production of humanized antibodies is 3D6; para [0012] - an alignment of the amino acid sequences of the light chain of mouse 3D6, humanized 3D6; para [0350] - The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130), and positions 234,235 and 237 in the heavy chain constant region are occupied by Ala, Ala and Ala respectively (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ala) indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generally, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/80382

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 89, Bais discloses a method of treating or effecting prophylaxis of a disease ((para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) characterized by amyloid deposits of A.beta. in the brain (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) in a patient having at least one ApoE4 allele (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4), comprising administering administering different regimes (para [0215] - exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1 -10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly; para [0217] - The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic; para [0215] - two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated); wherein each regime comprises administering an antibody to A.beta. to a patient (para [0216] - Intervals can also be irregular as indicated by measuring blood levels of antibody to A.beta). However, Basi does not specifically teach administering a first regime to the patient before vasogenic edema appears, and a second regime after vasogenic edema has resolved. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises administering a first regime to the patient before vasogenic edema appears, and a second regime after vasogenic edema has resolved, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to control the development of vasogenic edema in the Alzheimer's patients having at least one ApoE4 allele treated with antibody against A.beta., because Basi teaches a method of treating or effecting prophylaxis of a disease characterized by amyloid deposits of A.beta. in the brain in a patient having at least one ApoE4 allele, comprising administering different regimes, wherein each regime comprises administering an antibody to A.beta. to the patient, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to use different regimes for treating Alzheimer's patients having ApoE4 allele, therein the first regime is with reduced antibody or antibody activities to A.beta., and a second regime after vasogenic edema has resolved; wherein the first regime differs relative to the second regime in at least of (i) – (iii) below:
(i) the dose of the antibody is reduced;
(ii) the frequency of administration of the antibody is reduced;
(iii) the capacity of the antibody to clear amyloid deposits is reduced.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US68/80382

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 90, Basi discloses a method of treating or effecting prophylaxis of a disease ((para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) characterized by amyloid deposits of A.beta. in the brain (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) in a patient having at least one ApoE4 allele (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4), administering administering different regimes (para [0215] - exemplary treatment regimes entail administration once per every two weeks or once a month or once every 3 to 6 months. Exemplary dosage schedules include 1 -10 mg/kg or 15 mg/kg on consecutive days, 30 mg/kg on alternate days or 60 mg/kg weekly; para [0217] - The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic; para [0215] - two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated); wherein each regime comprises administering an agent that induces an antibody to A.beta. on administration to a patient (para [0191] - immune responses against amyloid deposits can also be induced by administration of nucleic acids encoding antibodies and their component chains used for passive immunization; para [0216] - Intervals can also be irregular as indicated by measuring blood levels of antibody to A.beta.). However, Basi does not specifically teach administering a first regime to the patient before vasogenic edema appears, and a second regime after vasogenic edema has resolved. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/.4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises administering a first regime to the patient before vasogenic edema appears, and a second regime after vasogenic edema has resolved, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to control the development of vasogenic edema in the Alzheimer's patients having at least one ApoE4 allele treated with antibody against A.beta, because Basi teaches a method of treating or effecting prophylaxis of a disease characterized by amyloid deposits of A.beta. in the brain in a patient having at least one ApoE4 allele, comprising administering different regimes, wherein each regime comprises administering an agent that induces an antibody to A.beta. on administration to a patient, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to use different regimes for treating Alzheimer's patients having ApoE4 allele, therein the first regime is with reduced inducing effect to antibody to A.beta., and a second regime after vasogenic edema has resolved; wherein the first and second regimes each comprise administering an agent that induces an antibody to A.beta. on administration to a patient; wherein the first regime differs relative to the second regime in at least of (i) - (iii) below:
(i) the dose of the agent is reduced;
(ii) the frequency of administration of the agent is reduced;
(iii) the capacity of the agent to clear amyloid deposits is reduced.

Regarding claim 91, Basi further discloses the method of claim 89 or claim 90, wherein the disease is Alzheimer's disease (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease; para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient).

Regarding claim 92, Basi further discloses the method of claim 89 or claim 90, wherein the patient has one or two ApoE4 alleles (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4).

Regarding claim 93, Basi further discloses the method of claim 89, wherein the diffement regimes each comprises administering an antibody that specifically binds to an epitope within residues 1-11 of A.beta. to the patient (pere [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta), and the antibody is administered at a dose of 0.15-1 mg/kg or 0.5-2 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg). Although Basi does not specifically teach regime with low dose is administered before vasogenic edema appears and and regime with higher dose is administered after vasogenic edema has resolved, this limitation is further obvious because because Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele (pg 1411; pg 1415, col 1, last para). One of ordinary skill in the art at the time the invention was made would have known to use regime with lower dose of an antibody to A.beta. before vasogenic edema appears for treating Alzheimer's patients having ApoE4 allele in order to increase does after resolving vasogenic edema. Therefore, the method of claim 89, wherein the first and second regimes each comprises administering an antibody that specifically binds to an epitope within residues 1-11 of A.beta. to the patient, and the antibody is administered at a dose of 0.15-1 mg/kg before vasogenic edema appears and 0.5-2 mg/kg after vasogenic edema has resolved.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US08/80382

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 106, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a population of patients (para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease), comprising
administering an antibody that specifically binds to an epitope within residues 1-11 of A.beta. to the patients (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta), wherein the antibody is administered at a dose of 0.15-1 mg/kg or a dose of 0.5-2.5 mg/kg (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg) in different patients of the population (para [0217] - The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic). However, Basi does not specifically teach wherein the antibody is administered at a dose of 0.15-1 mg/kg in patients of the population having one or two ApoE4 alleles and a dose of 0.5-2.5 mg/kg in patients of the population having zero ApoE4 alleles, and the mean dose is higher in the patients having zero ApoE4 alleles. Klnnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the methgod of Basi, wherein the method further comprises the antibody is administered at a dose of 0.15-1 mg/kg in patients of the population having one or two ApoE4 alleles and a dose of 0.5-2.5 mg/kg in patients of the population having zero ApoE4 alleles, and the mean dose is higher in the patients having zero ApoE4 alleles, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to use the regime comprising lower does of an antibody to A.beta to treat Alzheimer's patients having one or two copies of an ApoE4 allele to prevent the development of vasogenic edema from happening, because Basi teaches a method of treating or effecting prophylaxis of Alzheimer's disease in a population of patients, comprising
administering an antibody that specifically binds to an epitope within residues 1-11 of A.beta. to the patients, wherein the antibody is administered at a dose of 0.15-1 mg/kg or a dose of 0.5-2.5 mg/kg in different patients of the population, while Klnnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known to use regime comprising lower does of an antibody to A.beta. to treat Alzheimer's patients having ApoE4 allele.

Regarding claim 107, Basi further discloses the method of claim 106, wherein the antibody is a humenized form of a mouse 3D6 antibody (ATCC accession number PTA-5130) (para [0114] - the present invention features a humanized antibody to the N-terminus of A.beta. A particularly preferred starting material for production of humanized antibodies is 3D6; para [0012] - an alignment of the amino acid sequences of the light chain of mouse 3D6, humanized 3D6; para [0350] - The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130), and positions 234,235 and 237 in the heavy chain constant region are occupied by Ala, Ala and Ala respectively (para [0174] - Mutations on adjacent or close sites in the hinge link region (e.g., replacing residues 234, 236 or 237 by Ala) indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such as gly, ala), wherein positions are numbered by the ED numbering system (para [0171] - Typically the Kabat numbering system is used to indicate which amino acid residue(s) of the Fc region; Specification [0248] - The EU numbering system is conventional (see generelly, Kabat et al., Sequences of Protein of Immunological Interest, NIH Publication No. 91-3242, US Department of Health and Human Services (1991)).

Regarding claim 110, the reason discussed in claim 106 further support the method of claim 106, wherein the dose is 0.5 mg/kg in patients of the population having one or two ApoE4 alleles and 2 mg/kg in patients of the population having zero ApoE4 alleles.

Regarding claim 117, Basi discloses a method of effecting prophylaxis of a disease characterized by
deposits of A.beta. deposits in the brain of a patient (para [0035] - the invention features a method of preventing or treating an amyloidogenic disease, e.g., Alzheimer's disease; para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) comprising administering an effective regime of an agent that is en antibody to A.beta. to a patient, as discussed in claim 111. However, Besi does not specifically teaches wherein the method further comprising determining the number
of ApoE4 alleles in the patient. Klnnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele and associated copy numbers (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises determining the number of ApoE4 alleles in the patient, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to more effectively control the development of vasogenic edema in the Alzheimer's patients having different copy numbers of ApoE4 treated with antibody against A.beta, because Basi teaches a a method of effecting prophylaxis of a disease characterized by deposits of A.beta. deposits in the brain of a patient, comprising administering an effective regime of an agent that is an antibody to A.beta. to a patient, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele and associated copy numbers.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2008/050382

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 118, Basi discloses a method of treating or effecting prophylaxis of a disease ((para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease) characterized by amyloid deposits of Ap in the brain in a patient (para [0057] - Alzheimer's disease is an example of a "disease characterized by deposits of A.beta." or a "disease associated with deposits of A.beta.", e.g., in the brain of a subject or patient) comprising administering different regimes (para [0215] - usually 0.01 to 5 mg/kg, of the host body weight; para [0215] - For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg, preferably at least 1 mg/kg; para [0217] - The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic) each comprises administering an antibody to A.beta. to the patient (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta); monitoring the patient (para [0335] - Disease progression can also be monitored by MRI). However, Basi dose not specifically teches monitoring the patient for vasogenic edema. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease Immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises monitoring for vasogenic edema, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to control the development of vasogenic edema in the Alzheimer's patients treated with antibody against A.beta, because Basi teaches a a method of treating or effecting prophylaxis of a disease characterized by amyloid deposits of Ap in the brain in a patiant comprising administering different regimes, wherein each regime comprises administering an antibody to A.beta. to the patient, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele. One of ordinary skill in the art at the time the invention was made would have known maintaining the first regime if vasogenic edema does not appear; and administering a second regime to the patient if vasogenic edema does appear, wherein the second ragime comprises lower dose of antibody or antibody having lower activities, and
wherein the second regime differs relative to the first regime in at least one of (i) - (v) below:
(i) the dosa of the antibody is reducad;
(ii) the frequency of administration of the antibody is reduced;
(iii) a different antibody with reduced capacity to bind an Fcgamma receptor;
(iv) a different antibody with reduced capacity to bind C1q;
(v) the antibody to A.beta. is not administered; wherein the second regime is maintained at least for the duration of the vasogenic edema.

Regarding claim 119, Basi further discloses the method of claim 118, wherein the antibody in the first regime is an antibody that specifically binds to an epitope within residues 1-11 of A.beta. (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residuas 1-10 of A.beta).

Regarding claim 123, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population, comprising administering an antibody that specifically binds to an epitope within residues 1-11 of A.beta. and has mutations in the constant region that reduce binding to an Fc receptor
to the patient, wherein the antibody is administered at the same dose and/or frequency to each patient regardless of the number of ApoE4 alleles in the patient, as discussed in claim 21. However, Basi does not spacifically teach wherein the method further comprising a step of monitoring the patient for vasogenic edema. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephelitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edeme), which is associated with ApoE4 allele (pg 1411, lest para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises monitoring for vasogenic edema, based on the teaching of Kinnecom, to obtain the invention as claimed, in order control the development of vasogenic edema in the Alzheimer's patients having ApoE4 allele treated with antibody against A.beta, beceuse Basi teaches a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population, comprising administering an antibody thet specifically binds to an epitope within residues 1-11 of A.beta. and has mutations in the constant region that reduce binding to an Fc receptor to the patient, wherein the antibody is administered at the same dose and/or frequency to each patient regardless of the number of ApoE4 alleles in the patient, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US08/80382

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 124, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population, comprising administering an antibody to A.beta. to some of the patients in the population (para [0363] - the invention provides for the use of any of the antibodies to A.beta. described above in the treatment, prophylaxis or diagnosis of amyloidogenic disease), wherein patients in the population having zero ApoE4 alleles (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) receive the antibody (para [0201] - administering an effective dosage of an antibody that specifically binds to an epitope within residues 1-10 of A.beta). However, Basi does not specifically teach wherein patients in the population having two ApoE4 alleles do not receive the antibody. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein patients in the population having two ApoE4 alleles do not receive the antibody, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to avoid the development of vasogenic edema in the Alzheimer's patients having an ApoE4 allele treated with antibody against A.beta, because Basi teaches a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population, comprising administering an antibody to A.beta. to some of the patients in the population, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele.

Regarding claim 125, it is further obvious because the reason discussed in 124. Therefore, the method of claim 124, wherein patients in the population having ona ApoE4 allele do not receive the antibody.

Regarding claim 126, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population, comprising administering an agent that induces an antibody to A.beta. on administration to some of the patients in the population (para [0191] - Immune responses against amyloid deposits can also be induced by administration of nucleic acids encoding antibodies and their component chains used for passive immunization; para [0216] - Intervals can also be irregular as indicated by measuring blood levels of antibody to A.beta), wherein patients in the population having zero ApoE4 alleles (para [0208] - Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms; para [0208] - Other markers of risk are mutations in the presenilin genes and ApoE4) receive the agent (para [0191] - Immune responses against amyloid deposits can also be induced by administration of nucleic acids encoding antibodies and their component chains used for passive immunization; para [0216] - Intervals can also be irregular as indicated by measuring blood levels of antibody to A.beta etal). However, Basi does not specifically teach wherein patients in the population having two ApoE4 alleles do not receive the antibody. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edeme), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein patients in the population having two ApoE4 alleles do not receive the agent, based on the teaching of Kinnecom, to obtain the invention as claimed, in order to avoid the development of vasogenic edema in the Alzheimer's patients having an ApoE4 allele treated with agent inducing antibody against A.beta, beceuse Basi teaches a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population, comprising administering an agent that induces an antibody to A.beta. on administration to some of the patients in the population, while Kinnecom teaches Alzheimer's petients treated with antibodies against A.bete develop vasogenic edema, which is associated with ApoE4 allele.

Regarding claim 127, it is further obvious because the reason discussed in 124. Therefore, the method of claim 126, wherein patients in the population having one ApoE4 allele do not receive the agent.

Regarding claim 132, Basi discloses a method of treating or effecting prophylaxis of a disease characterized by A.beta. deposits in the brain of patient comprising administering an effective regime of a humanized antibody to A.beta. to the patient, es discussed in claim 128. Basi further teaches monitoring the patient by MRI (para [0335] - Disease progression can also be monitored by MRI). However, Basi does not specifically teach wherein the method further comprising monitoring the patient for vasogenic edeme. Kinnecom discloses a clinical study showing patients treated with antibodies against A.beta develop vasogenic edema (pg 1411, para 2: CAA also appears to have clinical, radiographic, and pathologic similarities to the meningoencephalitis developed by some patients with Alzheimer disease immunized to A.beta.; pg 1411, Abstract: A subset of patients with cerebral amyloid angiopathy (CAA), with signal properties suggesting vasogenic edema), which is associated with ApoE4 allele (pg 1411, last para - A candidate risk factor is the APOE 4/ 4 genotype; pg 1415, col 1, last para). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi and Kinnecom, to obtain the method of Basi, wherein the method further comprises monitoring patient for vasogenic edema by MRI, based on the teachings of Basi and Kinnecom, to obtain the invention as claimed, in order to control the development of vasogenic edema in the Alzheimer's patients treated with antibody against A.beta, because Basi teaches a a method of treating or effecting prophylaxis of a disease characterized by A.beta. deposits in the brain of patient comprising administering an effective regime of a humanized antibody to A.beta. to the patient, while Kinnecom teaches Alzheimer's patients treated with antibodies against A.beta develop vasogenic edema, which is associated with ApoE4 allele.

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Claims 48, 60, 66-70, 87, 94-95 and 108 lack an inventive step under PCT Article 33(3) as being obvious over Basi in view of Kinnecom, as above, and further in view of Tobinick.

Regarding claim 48, Basi and Kinnecom discloses a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, wherein the second antibody has reduced binding to an Fcgamma receptor as discussed in claim 41. Basi further discloses wherein the first antibody is 3D6 (para [0114] - the present invention features a humanized antibody to the N-terminus of A.beta. A particularly preferred starting material for production of humanized antibodies is 3D6), and the second antibody is an L234A, L235A, G237A variant of 3D6 (para [0171] - the antibodies of the invention can be modified to bind to only certain Fc receptors, or lack Fc receptor binding entirely, by deletion or alteration of the Fc receptor binding site located in the Fc region of the antibody; para [0174] - Mutations on adjacent or close sites in the hinge link region, e.g., replacing residues 234, 236 or 237 by Ala, indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity for the Fc.gamma.RI receptor; para [0013] - FIG. 2 depicts an alignment of the amino acid sequences of the heavy chain of mousa 3D6, humanized 3D6; Fig. 2). However, none of inventors specifically teach the antibody is bapineuzuab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimar's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, e humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Besi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the first antibody is bapineuzumab and the second antibody is an L234A, L235A, G237A variant of bapineuzumab, based on the teachings of Basi, Kinnecom, and Tobinick, to obtain the invention as claimed, in order to use the humanized monoclonal antibody Bapineuzumab as the first antibody administered to patients having zero copies of an ApoE4 allele, and an L234A, L235A, G237A variant of bapineuzumab as the second antibody administered to patients having one or two copies of an ApoE4 allele for treating or effecting prophylaxis of Alzheimer's disease in a patients of different population, because Basi and Kinnecom teach a method of treating or effecting prophylaxis of Alzheimer's disease in patients of different population by administering the first antibody 3D6 to patients having zero copies of an ApoE4 allele, and administering an L234A, L235A, G237A variant of 3D6, with reduced Fcgamma binding affinity, as the second antibody to patients having one or two copies of an ApoE4 allele, and Basi further teaches amino acid 234, 235, and 237 are convenient modification residues in Fc region (para [0174] - altered Fc region with altered binding affinity for Fc.gamma.RI as compared with the unmodified antibody. Such an antibody conveniently has a modification at amino acid residue 234, 235, 236, or 237) while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 60, Basi and Kinnecom disclose a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, wherein the patients in the population having one or two ApoE4 alleles are administered en antibody with reduced
capacity to induce a clearing response to amyloid deposits, as discussed in claim 40. However, none of inventors specifically teaches wherein the antibody with reduced capacity to induce a clearing response to amyloid deposits relative to bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimar's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody with reduced capacity to induce a clearing response to amyloid deposits relative to bapineuzumab, based on the teachings of Basi, Kinnecom, and Tobinick, to obtain the invention as claimed, in order to use the antibody with reduced capacity to induce a clearing response to amyloid deposits relative to bapineuzumab to treat Alzheimer's patients having one or two copies of an ApoE4 allele, because Besi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic diseese characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, wherein the patients in the population having one or two ApoE4 alleles are administered an antibody with reduced
capacity to induce a clearing response to amyloid deposits, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

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Regarding claim 66, Basi and Kinnecom disclose a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering an antibody to A.beta. to a patient, wherein the antibody has human IgG1 isotype as discussed in claim 65. However, none of inventors specifically teaches wherein the antibody is bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody is bapineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed, in order to use the antibody bapineuzumab to treat or effect prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, because Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering an antibody to A.beta. to a patient, wherein the antibody has human IgG1 isotype, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humenized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 67, Basi and Kinnecom disclose a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering antibody has a reduced capacity to induce a clearing response to amyloid deposits to the patients in the population having one or two ApoE4 alleles, as discussed in claim 40. However, none of inventors specifically teaches wherein the antibody with reduced capacity to induce a clearing response to amyloid deposits relative to bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnacom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody with reduced capacity to induce a clearing response to amyloid deposits relative to bapineuzumab, based on the teachings of Basi, Kinnecom, and Tobinick, to obtain the invention as claimed, in order to use the antibody with reduced capacity to induce a clearing response to amyloid deposits relative to bapineuzumab to treat Alzheimer's patients having one or two copies of an ApoE4 allele, because Basi and Kinnecom teach a method of treating or affecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering antibody has a reduced capacity to induce a clearing response to amyloid deposits to the patients in the population having one or two ApoE4 alleles, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 68, Basi and Kinnecom disclose a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering antibody has a reduced capacity to induce a clearing response to amyloid deposits to the patients in the population having one or two ApoE4 alleles, as discussed in claim 40. Basi further discloses wherein the antibody has e reduced capacity to induce a clearing response to amyloid deposits to the patients is an L234A, L235A, G237A variant (para [0174] - Mutations on adjacent or close sites in the hinge link region, e.g., replacing residues 234, 236 or 237 by Ala, indicate that alterations in residues 234, 235, 236, and 237 at least affact affinity; para [0105] - By conservative substitutions is intended combinations such es gly, ale; para [0013] - FIG. 2 dapicts an alignment of tha amino acid sequences of the heavy chain of mouse 3D6, humanized 3D6; Fig. 2). However, none of inventors specifically teach wherein the antibody is an L234A, L235A, G237A variant of bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnacom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody has a reduced capacity to induce a clearing response to amyloid deposits to the patients is an L234A, L235A, G237A variant of bapineuzumab, based on the teachings of Basi, Kinnecom, and Tobinick, to obtain the invention as claimed, in order to use the antibody, an L234A, L235A, G237A variant of bapineuzumab, with reduced capacity to treat Alzheimer's patients having one or two copies of an ApoE4 allele, becausa Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering antibody has a reduced capacity to induce a clearing response to amyloid deposits to the patients in the population having one or two ApoE4 alleles, and Basi further teaches an L234A, L235A, G237A variant of an antibody with reduced capacity, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

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Regarding claim 69, Basi and Kinnecom disclose a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, wherein the patients in the population having one or two ApoE4 alleles are administered an antibody with reduced
capacity to induce a clearing response to amyloid deposits, as discussed in claim 40. Basi further discloses a less preferred humanized 266 antibody (para [0075] - Less preferred antibodies include those binding to epitopes with residues 10-15, 15-20, 25-30, 10-20, 20, 30, or 10-25 of A.beta; para [0010] - humanized antibodies having improved binding affinities and/or reduced immunogenicity, when used as therapeutic reagents; Specification: para [00201] - Another exemplary antibody is a humanized 266 antibody or variant thereof. The 266 antibody binds to an epitope between residues 13-28 of A.beta) because some of them might lack of activities (para [0075] - certain antibodies to epitopes within residues 10-18, 16-24, 18-21 and 33-42 lack activity) can be used in combinations with other antibodies (para [0075] - multiple monoclonal antibodies having binding specificities to different epitopes are used. Such antibodies can be administered sequentially or simultaneously). However, none of inventors specifically teach bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody is Bapineuzumab, and antibody with reduced capacity is humanized 226 antibody, based on the teachings of Basi, Kinnecom, and Tobinick, to obtain the invention as claimed, in order to use the Bapineuzumab to treat Alzheimer's patients having zero ApoE4 allele, and use humanized 226 antibody with reduced capacity to treat Alzheimer's patients having one or two copies of an ApoE4 allele, because Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, wherein the patients in the population having one or two ApoE4 alleles are administered an antibody with reduced capacity to induce a clearing response to amyloid deposits, Basi further teach humanized 226 antibody is an antibody with reduced capacity, while Tobinick teaches a method of treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta. Although none of inventors specifically teaches patients with one or two ApoE4 alleles are administered 1-3 doses of humanized 266 antibody following by subsequent doses of bapineuzumab and patients with zero ApoE4 alleles are administered the same total number of doses but all with bapineuzumab, this limitation is further obvious because Basi teaches multiple monoclonal antibodies having binding specificities to different epitopes can be administered sequentially (para [0075]), it is clinical routine practice to adjust the used of antibodies according to patients' initial response after initial treatment. Therefore, to Alzheimer's patients having one or two ApoE4 alleles, the regime can be: administered 1-3 doses of humanized 266 antibody following by subsequent doses of bapineuzumab.

Regarding claim 70, Basi and Kinnecom disclose a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, wherein the patients in the population having one or two ApoE4 alleles are administered an antibody with reduced
capacity to induce a clearing response to amyloid deposits, as discussed in claim 40. Basi further discloses a less preferred humanized 266 antibody (para [0075] - Less preferred antibodies include those binding to epitopes with residues 10-15, 15-20, 25-30, 10-20, 20, 30, or 10-25 of A.beta; para [0010] - humanized antibodies having improved binding affinities and/or reduced immunogenicity, when used as therapeutic reagents; Specification: para [00201] - Another exemplary antibody is a humanized 266 antibody or variant thereof. The 266 antibody binds to an epitope between residues 13-28 of A.beta) because some of them might lack of activities (para [0075] - certain antibodies to epitopes within residues 10-18, 16-24, 18-21 and 33-42 lack activity) can be used in combinations with other antibodies (para [0075] - multiple monoclonal antibodies having binding specificities to different epitopes are used. Such antibodies can be administered sequentially or simultaneously). However, none of inventors specifically teach bapineuzumab, or patients with one or two ApoE4 alleles are administered humanized 266 antibody and patients with zero ApoE4 alleles are administered bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody is Bapineuzumab, and antibody with reduced capacity is humanized 226 antibody, based on the teachings of Basi, Kinnecom, and Tobinick, to obtain the invention as claimed, in order to use the Bapineuzumab to treat Alzheimer's patients having zero ApoE4 allele, and use humanized 226 antibody with reduced capacity to treat Alzheimer's patients having one or two copies of an ApoE4 allele, because Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering different regimes to different patients in the population, wherein the patients in the population having one or two ApoE4 alleles are administered an antibody with reduced capacity to induce a clearing response to amyloid deposits, Basi further teach humanized 226 antibody is an antibody with reduced capacity, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

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Regarding claim 87, Basi and Kinnecom disclose a method of treating or effecting prophylaxis of a patient for a disease characterized by amyloid deposits of A.beta. in the brain, comprising
administering to a patient with at least one ApoE4 allele an antibody to A.beta. as discussed in claim 85. However, none of inventors specifically teaches wherein the antibody is bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention wes made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody is bapineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed, in order to use the antibody bapineuzumab to treat Alzheimer's patients having at leaset one ApoE4 allele, because Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering to a patient with at least one ApoE4 allele an antibody to A.beta, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 94, Basi and Kinnecom disclose a method of treating or effecting prophylaxis of a patient for a disease characterized by amyloid deposits of A.beta. in the brain, comprising
administering to a patient with at least one ApoE4 allele an antibody to A.beta. as discussed in claim 89. However, none of inventors specifically teaches wherein the antibody is bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disordere are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humenized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Besi and Kinnecom, wherein the entibody is bepineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed, in order to use the antibody bapineuzumab to treat Alzheimer's patients heving at leaset one ApoE4 allele, because Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: edministering to e patient with at least one ApoE4 allele an entibody to A.beta, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Regarding claim 95, Basi and Kinnecom disclose a method of treating or effecting prophylaxis of a patient for a disease characterized by amyloid deposits of A.beta. in the brain, comprising
administering to a petient with at least one ApoE4 allele an antibody to A.beta., wherein the first regime comprising antibody heving a reduced capecity to induce a clearing response to amyloid deposits to the patients is administered to the patient before vasoganic edema appears, as discussed in claim 89. Basi further discloses wherein the antibody has a reduced capacity to induce a clearing response to amyloid deposits to the patients is an L234A, L235A, G237A verient (para [0174] - Mutations on adjacent or close sites in the hinge link region, e.g., replacing residues 234, 236 or 237 by Ala, indicate that alterations in residues 234, 235, 236, and 237 at least affect affinity; para [0105] - By conservative substitutions is intended combinations such es gly, ela; para [0013] - FIG. 2 depicts an alignmant of the amino acid sequences of the heavy chain of mouse 3D6, humanized 3D6; Fig. 2). However, none of inventors spacifically teach wherein the antibody is an L234A, L235A, G237A variant of bapineuzumeb. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease, Humans with these disordars are amenable to treatment utilizing perispinal administration without direct intrathecal injection of lerge molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody egainst A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, e humanized monoclonal entibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody has e reduced capacity to induce a clearing response to amyloid deposits to the patients is an L234A, L235A, G237A variant of bapineuzumab, based on the teechings of Basi, Kinnecom, and Tobinick, to obtain the invention as claimed, in order to comprise the entibody, an L234A, L235A, G237A variant of bapineuzumab, with reduced capacity in the first regime to treat Alzheimer's patients having at least one ApoE4 allele, because Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. in the brain, comprising: administering to a patient with at least one ApoE4 allele an antibody to A.beta., wherein the first regime comprising antibody having a reduced capacity to induce a clearing response to amyloid deposits to the patients is administered to the patient before vasogenic edema appears, and Basi further teaches an L234A, L235A, G237A variant of an antibody with reduced capacity, while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

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Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 108, Basi and Kinnecom disclose a method of treating or effecting prophylaxis of a patient for a disease characterized by amyloid deposits of A.beta. in the brain, comprising
administering to a patient an antibody to A.beta. as discussed in claim 106. However, none of inventors specifically teaches wherein the antibody is bapineuzumab. Tobinick discloses a method of treating Alzheimer's Disease (para [0267] - Dementia. This category includes, but is not limited to Alzheimer's Disease,. Humans with these disorders are amenable to treatment utilizing perispinal administration without direct intrathecal injection of large molecules, including but not limited to anti-amyloid antibodies) using a humanized monoclonal antibody against A.beta., wherein the monoclonal antibody is Bapineuzumab (para [0019] - antibodies against beta-amyloid; and, specifically, Bapineuzumab, a humanized monoclonal antibody to A-beta). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Basi, Kinnecom, and Tobinick, to obtain the method of Basi and Kinnecom, wherein the antibody is bapineuzumab, based on the teaching of Tobinick, to obtain the invention as claimed, In order to use the antibody bapineuzumab to treat Alzheimer's patients, because Basi and Kinnecom teach a method of treating or effecting prophylaxis in a population of patients of an amyloidogenic disease characterized by amyloid deposits of A.beta. In the brain, comprising: administering to a patient an antibody to A.beta., while Tobinick teaches a method of treating treating Alzheimer's Disease using a humanized monoclonal antibody, Bapineuzumab, against A.beta.

Claims 88, 96, 100, 105, 109, 120, 122, and 143 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an amino acid saquence having 100 % homology to SEQ ID NO: 66 or SEQ ID NO: 67.

Regarding claim 88, Basi and Kinnecom disclose a method of treating or effecting prophylaxis of a patient for a disease haracterized by amyloid deposits of A.beta in the brain, comprising
administering to a patient with at least one ApoE4 allele an antibody to an epitope within residue 1-11 of A.beta, and monitoring the patiant for vasogenic edema by MRI, as discussed in claim 85. US 2006/0193850 A1 to Warne et al. (hereinafter 'Warne') discloses an antibody is an variant of bapineuzumab comprising a humanized light chain having an amino acid sequence comprising SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior art specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Para [0149]).

Regarding claim 96, Basi and Kinnecom disclose a method of treating or effecting prophylaxis of a patient for a disease characterized by amyloid deposits of A.beta. in the brain, comprising
administering to a patient with at least one ApoE4 allele an antibody to A.beta., wherein the first regima comprising antibody having a reduced capacity to induce a clearing response to amyloid deposits to the patients is administered to the patient before vasogenic edama appears, as discussed in claim 89. Warne discloses an antibody is an variant of bapineuzumab comprising a humanized light chain having en emino acid sequence comprising SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior art specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Pare [0149]).

Regarding claim 100, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patiant of claim 97, as discussed ebove. Warne discloses an antibody is an variant of bapineuzumab comprising a humanized light chain having an amino acid saquence comprising SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior art specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Para [0149]).

Regarding claim 105, Besi discloses e method of treating or effecting prophylaxis of Alzhaimer's disease in a patient of claim 102, as discussed ebove. Warne discloses en antibody is an variant of bapineuzumab comprising a humanized light chain having an amino acid sequence compriesng SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior ert specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Para [0149]).

Regarding claim 109 Basi and Kinnecom disclose a method of treating or effecting prophylaxis of Alzheimer's disease in a population of patients of claim 106, as discussed ebove. Werne discloses an antibody is an variant of bapineuzumab comprising a humanized light chain having an amino acid sequence comprising SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior art specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Para [0149]).

Regarding claim 120, Basi and Kinnecom disclose e method of treating or effecting prophylaxis of a disease characterized by emyloid deposits of A.beta. in the brain in a patient comprising
administering a first regime and a second regime each comprises administering an antibody to A.beta. to the patient as discussed in claim 118. Tobinick discloses the first antibody is bapineuzumab. Warne discloses an antibody is an variant of bapineuzumab comprising a humanized light chain having an amino acid sequence comprising SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior art specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Para [0149]).

**********Continued in supplemental Form**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/80382

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 122, Basi discloses a method of treating or effecting prophylaxis of Alzheimer's disease in a patient population, comprising administering an antibody that specifically binds to an epitope within residues 1-11 of A.beta. and has mutations in the constant region that reduce binding to an Fcgamma receptor, as discussed in claim 121. Warne discloses an antibody is an variant of bapineuzumab comprising a humanized light chain having an amino acid sequence comprising SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior art specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Para [0149]).

Regarding claim 143, Warne discloses a humanized antibody comprising a humanized light chain having an amino acid sequence comprising SEQ ID NO:48 (para [0149] - SEQ ID NO: 1, which is 100% identical to SEQ ID NO: 48). However, none of the prior art specifically teaches SEQ ID NO: 66 or SEQ ID NO: 67, both of them are 99.4% identical to SEQ ID NO: 2 of Warne (Para [0149]).

Claims 1-3, 10-60, 64-133, 143, and 145-146 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]: "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.